Involvement of BDNF in age-dependent alterations in the hippocampus

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It is known since a long time that the hippocampus is sensitive to aging. Thus, there is a reduction in the hippocampal volume during aging. This age-related volume reduction is paralleled by behavioral and functional deficits in hippocampus-dependent learning and memory tasks. This age-related volume reduction of the hippocampus is not a consequence of an age-related loss of hippocampal neurons. The morphological changes associated with aging include reductions in the branching pattern of dendrites, as well as reductions in spine densities, reductions in the densities of fibers projecting into the hippocampus as well as declines in the rate of neurogenesis. It is very unlikely that a single factor or a single class of molecules is responsible for all these age-related morphological changes in the hippocampus. Nevertheless, it would be of advantage to identify possible neuromodulators or neuropeptides that may contribute to these age-related changes. In this context, growth factors may play an important role in the maintenance of the postnatal hippocampal architecture. In this review it is hypothesized that brain-derived neurotrophic factor (BDNF) is a factor critically involved in the regulation of age-related processes in the hippocampus. Moreover, evidences suggest that disturbances in the BDNF-system also affect hippocampal dysfunctions, as e.g. seen in major depression or in Alzheimer disease.

Keywords: aging, hippocampus, brain-derived neurotrophic factor, depression, dendritic spines, neurogenesis

THE AGED HIPPOCAMPUS

The hippocampal formation, a brain structure involved in spatial memory, exhibits marked functional decline with aging in humans, monkeys, and rodents (Greene and Naranjo, 1987; Walker et al., 1988; Lee et al., 1994; Rapp and Heindel, 1994; Rapp and Gallagher, 1996; Driscoll et al., 2003). Since a long time it is well established that there is a reduction in the hippocampal volume during aging in healthy adults (**Figure 1**). Several studies, using e.g. magnetic resonance imaging (MRI), confirmed the age-related reduction in hippocampal volume (Convit et al., 1995; Mu et al., 1999; Driscoll et al., 2003; Malykhin et al., 2008; Raz et al., 2010). This age-dependant shrinkage of the hippocampus was found to be accelerated with time (Raz et al., 2010; Zhang et al., 2010). Age-related deficits could e.g. be observed in the performance on hippocampus-dependent tasks in humans and it has been shown that these deficits were accompanied by decreased hippocampal volume (Driscoll et al., 2003). This hippocampal shrinkage has been attributed to hippocampal atrophy and to neuronal losses or decreases in neuronal densities (Driscoll et al., 2003). In early morphometric studies that determined the number of human hippocampal neurons directly, it was found that normal aging was accompanied by a more or less pronounced gradual loss of hippocampal neurones (Ball, 1977; Mani et al., 1986). These as well as other results suggest that the hippocampus undergoes structural and biochemical changes during normal aging.

These alterations in the hippocampus during aging are paralleled by behavioral and functional deficits in hippocampus-dependent learning and memory tasks (Rosenzweig and Barnes, 2003). The hippocampus is involved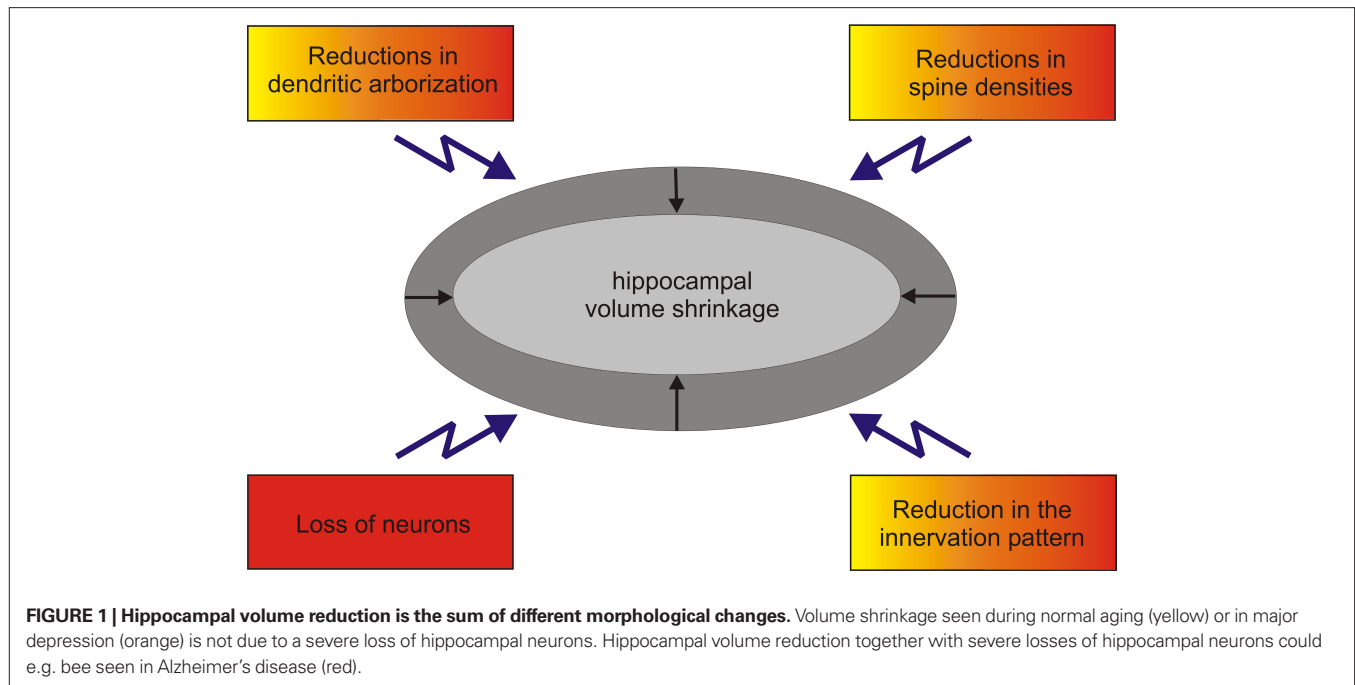, e.g. in spatial learning tasks and both, aged humans and aged rodents exhibit spatial memory deficits (Barnes, 1987). In rodents, age-related impairments have been described for hippocampus-dependant spatial as well as for contextual learning tasks, such as water maze and fear conditioning (Ward et al., 1999; Rosenzweig and Barnes, 2003). Moreover, it has been shown that learning deficits in aged rats are accompanied by a decrease in hippocampal volume (Sykova et al., 2002).

Spatial navigation is a complex cognitive skill that involves the hippocampus of humans and it is known that navigation, as an aspect of cognitive function, is vulnerable to aging (Moffat, 2009). In this context, it is important to note that older individuals required more time to form a cognitive map of the environment than young individuals (Iaria et al., 2009). In addition, way-finding has been associated with the hippocampus and also for way-finding it has been shown that aging effects recall of landmarks, and the recognition of environmental scenes (Head and Isom 2010). Interestingly, the age-related changes in way-finding were significantly associated with hippocampal volume changes (Head and Isom 2010).

Thus, it can be concluded that aging is often accompanied by hippocampal-dependent learning and memory problems, many of which resemble deficits associated with hippocampal damage. Despite such evidences that age-related dysfunctions are associated with reductions in the volume of the hippocampal formation, the cellular and morphological basis of this decline is largely unknown.

ALTERATIONS IN THE INNERVATION OF THE AGED HIPPOCAMPUS

Since there is an association between hippocampal volume reductions and declines in hippocampus dependent learning and memory function, other structural changes may be related to the dysfunction

FIGURE 1 | Hippocampal volume reduction is the sum of different morphological changes. Volume shrinkage seen during normal aging (yellow) or in major depression (orange) is not due to a severe loss of hippocampal neurons. Hippocampal volume reduction together with severe losses of hippocampal neurons could e.g. bee seen in Alzheimer's disease (red).

of the aged hippocampus. The analysis of the aged hippocampus revealed indeed several structural changes that may be associated with reductions in the hippocampal volume.

During aging, there is e.g. an increase in the density of fragments of degenerated axons within the hippocampus (von Bohlen und Halbach and Unsicker, 2002). This increased density of degenerated fibers is indicative for a loss of fibers within the aged hippocampus. Thus, a reduction in fibers projecting into the aged hippocampus may contribute to the volume reductions in the aged hippocampus. The hippocampal formation is innervated by cortical and subcortical areas; however, within the aged forebrain, cell losses in cortical areas that project to the hippocampus, as e.g. the entorhinal cortex, seem not to represent a hallmark of aging (Gazzaley et al., 1997; Merrill et al., 2001).

The noradrenergic system projects into the hippocampal formation. The source for these fibers is located in the locus coeruleus (Robinson et al., 1977; Ader et al., 1980). Data concerning a possible loss of neurons within the locus coeruleus are not consistent; thus, no cell loss as well as cell losses in that nucleus have been reported in the context of aging (Lohr and Jeste, 1988; Chan-Palay and Asan, 1989; Manaye et al., 1995; Ohm et al., 1997). Nevertheless, there is evidence to suggest that there is a decline in the density of noradrenergic fibers innervating the aged dentate gyrus (DG) (Ishida et al., 2000). A further system that projects into the hippocampus is the dopaminergic (DAergic) system. Concerning the DAergic system and the hippocampus, it is known that the hippocampus is innervated by DAergic neurons, located in the ventral tegmental area and the substantia nigra (Gasbarri et al., 1994). This DAergic mesolimbic system is sensitive to aging (Miguez et al., 1999) and might be implicated in age-related impairments (Barili et al., 1998). Indeed, the total number of DAergic neurons in the substantia nigra decreases with age (Naoi and Maruyama, 1999; Siddiqi

et al., 1999). Based on that, it may be possible that there is an age-related loss of DAergic fibers within the hippocampus. One enzyme, tyrosine-hydroxylase (TH) is involved in the biosynthesis of both, dopamine and noradrenalin. TH is located not only in the soma, but also in the processes of DAergic and noradrenergic neurons. Using TH-immunohistochemistry, it has been shown that there is an age-related decline in the density of TH-positive fivers within the DG (von Bohlen und Halbach and Unsicker, 2003). Along this line, it has been shown that aged rats display reduced concentration of dopamine and noradrenalin in the hippocampus (Miguez et al., 1999).

Serotonin, another transmitter, is also produced in areas that are sensitive to aging. For example, it has been shown that the numbers of serotonergic neurons within different raphe nuclei of rats decrease during aging (Tatton et al., 1991; Lolova and Davidoff, 1992). This age-related cell loss might be responsible for the marked decrease in the density of serotonergic fibers within the DG (Nishimura et al., 1995).

Furthermore, the hippocampus is also innervated by cholinergic fibers that stem from the septum. These septo-hippocampal projections are e.g. involved in the modulation of short-term spatial (working) memory processes (Everitt and Robbins, 1997). Whereas the number and size of cholinergic neurons within the septum is not altered in the context of aging (Ypsilanti et al., 2008; Niewiadomska et al., 2009), there is a marked decrease in cholinergic fibers projecting into the hippocampus (Gilad et al., 1987; Ypsilanti et al., 2008; Niewiadomska et al., 2009), indicating that cholinergic axonal degeneration occurs during aging.

Thus, axonal degeneration in the hippocampus is likely to be due to reductions in the amount of fibers that supply the hippocampus with different transmitters. The loss of these fibers could contribute to hippocampal dysfunctions and may contribute to volume losses of the aged hippocampus.

NEUROGENESIS AND THE AGED HIPPOCAMPUS

Neurogenesis has long been believed only to occur during brain development. However, in some areas within the forebrain, namely the subventricular zone and the DG, neurogenesis persists in the postnatal brain. The rate of neurogenesis within the DG can be altered under various physiological and pathophysiological conditions. Interestingly, neurogenesis within the DG seems to be linked to hippocampus-dependent learning and memory.

Neurogenesis within the DG is increase in mice that were housed in an enriched environment (Kempermann et al., 1997). Increased neurogenesis within the DG is also observed in a variety of hippocampus-dependent learning and memory tasks (Drapeau et al., 2003; Ming and Song, 2005; Snyder et al., 2005). Furthermore, enriched environment not only increases neurogenesis in the DG, but also improves spatial memory (Nilsson et al., 1999). Thus, functional neurogenesis seems to have a profound impact upon neuronal plasticity within the hippocampus. Along this line, it has also been shown that long-term potentiation (LTP), a well characterized form of synaptic plasticity believed to play a critical role in memory formation, stimulates neurogenesis within the hippocampus (Bruel-Jungerman et al., 2006).

Since the hippocampus exhibits marked functional decline with aging, it could be speculated that neurogenesis within the aged DG is altered. Indeed, it has been shown that neurogenesis is drastically reduced in aged animals (e.g. rats Kuhn et al., 1996 and monkeys Gould et al., 1999). Neurogenesis therefore seems to be linked to hippocampal functions and an age-related decline in hippocampal functions seems to be accompanied by a reduction in neurogenesis. Given that neurogenesis occurs throughout the postnatal life, one would expect that the DG would increase in size during adulthood and that therefore the number of granule cells is increased in aged animals as compared to adult animals. However, this is not the case. Granule cell number of the DG do not increase with age (Rapp and Gallagher, 1996; Rasmussen et al., 1996; von Bohlen und Halbach and Unsicker, 2002), indicating that proliferation is balanced by cell death. Thus, not the addition of new neurons into the DG seemed to be linked to hippocampal functions, but the rate of the turnover of granule cells within the DG. Based on that, the reduced rate of neurogenesis within the aged DG seems not to contribute to volume reductions in the aged hippocampus.

AGE-RELATED CHANGES IN THE MORPHOLOGY OF NEURONS IN THE AGED HIPPOCAMPUS

Aside from age-related changes in the innervation pattern of the hippocampus, other structural changes may contribute to the volume reductions seen in the aged hippocampus. These structural changes may be related to the number of neurons within the aged hippocampus (see "Age-related changes in neuronal numbers in the aged hippocampus") or may be associated directly with the neurons located in the aged hippocampus. Structural changes of individual neurons in the aged hippocampus could e.g. be observed in altered branching patterns of neurons.

Concerning the DG, it has been described that volume fraction and surface area of dendritic shaft profiles are significantly decreased in senescent rats, relative to young adults (Geinisman et al., 1978) as well as the number of synapses (Bondareff, 1979). A morphometric analyses showed that cells from aged monkeys had significantly reduced vertical dendritic extents and distal dendritic branching, but increased proximal dendritic branching. However, the total dendritic length, number of dendritic branch points, and total segment number did not differ significantly from cells in the DG of young monkeys (Luebke and Rosene, 2003).

Concerning area CA1 of the hippocampus, a marked age-related reduction (nearly 40%) in the dendritic branch profiles (located in the stratum lacunosum-moleculare) of CA1 pyramidal neurons has been found that is accompanied by a marked decrease in the total volume fraction and total surface of dendrites per volume neuropil (Lolova, 1989). Somewhat comparable to the results obtained for area CA1, neurons located in subiculum also show reductions in their dendritic complexity (Uemura, 1985).

The dendrites of the hippocampal pyramidal and granular neurons are covered by small protrusions known as dendritic spines. Dendritic spines – at least in area CA1 – are the predominant site of excitatory synapses in the hippocampus (Megias et al., 2001). The density of dendritic spines is related to the amount of connectivity between the neurons with the dendritic spines and the axons from other neurons that built up synaptic contacts (von Bohlen und Halbach, 2009). One role of the dendritic spines is to establish and to maintain these connections. In addition, these small structures seem also to be involved in other functions, since they compartmentalize calcium and other signaling components that are involved in synaptic efficacy (Fiala et al., 2002). Thus, it is not surprisingly that dendritic spines are thought to play a role in neuronal plasticity. Indeed, some forms of learning have been shown to increase the number of dendritic spines (Geinisman, 2000; Yuste and Bonhoeffer, 2001; Nimchinsky et al., 2002; Leuner et al., 2003).

It is thought that the spine densities reflect the excitatory input density (Konur et al., 2003), since some forms of learning as well as hippocampal LTP have been associated with increased spine densities in the hippocampus (Engert and Bonhoeffer, 1999; Muller et al., 2000; Leuner and Shors, 2004). Moreover, LTP has been shown to promote the formation of new, mature, and probably functional synapses (Toni et al., 1999).

Thus, it may be speculated that dendritic spines might be altered in the time-course of aging in the whole hippocampus or within specific hippocampal sub-regions. No difference in spine densities have been detected within the DG of aged rats (Curcio and Hinds, 1983) as well as no changes in spine densities have been found in apical dendrites of CA1 neurons in aged rats (Lolova et al., 1989; Markham et al., 2005). Likewise, no age-related changes have been observed in spine densities of dendrites of the DG or of apical dendrites of area CA1 in mice (von Bohlen und Halbach et al., 2006b, 2008). In contrast, age-related reductions in spine numbers of hippocampal CA1 neurons have been noted by comparing senescence-accelerated mice (SAMP1TA/Ngs) at an age of 5 and 7 months (Kawaguchi et al., 1995). By comparing young adult (3-months-old) and aged (27-month-old) rats, spine densities of both basal and apical dendrites of CA1 have been found to be decreased in the old rats (Nunzi et al., 1987). Concerning mice, it has been shown that there is an age-related impairment in spatial learning as well as a decrease in the densities of basal dendrites of area CA1 (von Bohlen und Halbach et al., 2006b). In this context it is of interest to note that basal dendrites of area CA1 display an increase in spine densities, e.g. after spatial learning in rats (Moser et al., 1994). The observed age-related changes in dendritic spines may contribute to age-related impairments in synaptic plasticity,

including deficits in LTP. These alterations may impair the encoding of memories and thus may contribute to cognitive deficits observed in aged mammals (Rosenzweig and Barnes, 2003). Altered synaptic plasticity may also change the dynamic interactions among cells in hippocampal networks, causing deficits in the storage and retrieval of information about the spatial organization of the environment (Rosenzweig and Barnes, 2003). Thus, loss of dendritic spines during normal aging mainly occurs in area CA1, but nevertheless has a profound effect upon neuronal plasticity and seems to represent a morphological correlate of age-dependent declines in neuronal plasticity and hippocampus-dependent functions.

AGE-RELATED CHANGES IN NEURONAL NUMBERS IN THE AGED HIPPOCAMPUS

Loss of neurons in the forebrain has been widely viewed as a hallmark of normal aging (Landfield et al., 1992). Indeed, early morphometric studies provided evidence that normal aging is accompanied by a more or less pronounced gradual loss of hippocampal neurons (Ball, 1977; Mani et al., 1986). However, cell counting and estimation of neuronal densities is not trivial, since – among others – cutting artifacts, tissue artifacts, and other factors could bias the results. The development of unbiased stereological counting rules (Sterio, 1984; Gundersen et al., 1999; West, 1999) has enabled scientists to estimate neuronal numbers more precisely. By using stereological counting rules, no significant cell losses in the DG or in the pyramidal layers of the hippocampal areas CA1–CA3 have been detected (West, 1993; Rapp and Gallagher, 1996; Rasmussen et al., 1996; Calhoun et al., 1998; von Bohlen und Halbach and Unsicker, 2002). Thus, cell loss in the hippocampal formation seems not to represent the cellular basis for volume shrinkage of the aged hippocampal formation.

In summary, volume reduction of the aged hippocampus is not an event that can be attributed to a single parameter. Instead, volume reductions seem to be the sum of different morphological changes (reduction in the innervation pattern of the hippocampus; changes in the branching pattern of distinct neuronal populations within the hippocampus; reduction of spine densities) that all contribute to the hippocampal volume reduction in the context of aging.

It is very unlikely that a single factor or a single class of effector molecules is responsible for all these age-related morphological changes in the hippocampus. Nevertheless, it would be of advantage to identify possible neuromodulators or neuropeptides that may contribute to these age-related changes. Such a substance should meet at least some of the following requirements:

1) its expression should be altered in the context of aging
2) it should influence directly hippocampal neurons (branching patterns and/or dendritic spines of hippocampal neurons)
3) it should have an impact upon transmitter systems projecting to the hippocampal formation
4) it should have an impact upon neuronal plasticity
5) it should have an impact upon hippocampal volume

In this context, a family of trophic factors can be of interest, since this family of neuropeptides meets several of these criteria. Growth factors not only play a role during development, but several of them are also expressed in the postnatal brain, along with their cognate receptors. These factors, as e.g. the neurotrophins are involved in the maintenance of the architecture of the postnatal brain as well as they play a role in neuronal plasticity.

BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)

The family of neurotrophins consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and neurotrophin 4 (NT4). The neurotrophins bind to specific receptors that belong to the class of the Trk family of tyrosine protein kinase receptors. NGF specifically recognizes trkA, whereas BDNF and NT4 specifically activate trkB receptors. NT3, finally, primarily activates trkC receptors (**Figure 2**). In addition, all the neurotrophins can signal through a low-affinity receptor (which is structurally unrelated to the trk receptors), known as p75 receptor (Barbacid, 1994; Teng and Hempstead, 2004). In the context of age-related structural changes within the hippocampus, BDNF and its receptors may be of particular interest.

AGE-RELATED EXPRESSION OF BDNF

Levels of BDNF are not constant during the postnatal period. However, whether BDNF is up- or down-regulated in the context of aging seems to be region-dependent and species specific. It has been described that BDNF increases in the murine hippocampus during normal aging, but not during aging of mice with pathological changes (Katoh-Semba et al., 1998), whereas in aged rats a decline in hippocampal BDNF levels, as compared to young adult rats, has been observed (Karege et al., 2002). In aged monkeys (26, 30, and 32 years), the intensity of BDNF-immunoreactivity has been found to decline in cell bodies and dendrites of the neurons in the hippocampal formation (Hayashi et al., 2001). In humans, BDNF levels in plasma have been found to decrease with increasing age (Lommatzsch et al., 2005), but within the human hippocampus, levels of BDNF mRNA seem not to change significantly with
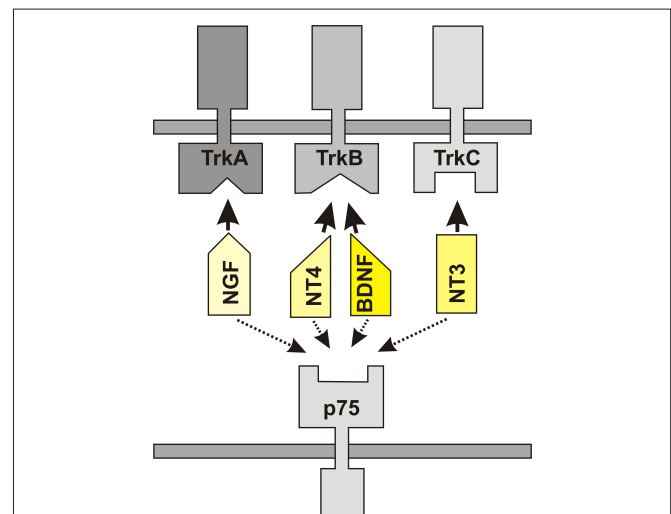
FIGURE 2 | The family of neurotrophins consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and neurotrophin 4 (NT4). NGF specifically binds to trkA receptors, BDNF and NT4 specifically bind to trkB and NT3 primarily activates trkC receptors. All these neurotrophins also bind and signal through the low-affinity receptor p75.

age (Webster et al., 2006), but the levels of trkB mRNA decreased over the life span (Webster et al., 2006). In accordance with these results, it has been shown that the levels of trkB decrease in the rat hippocampus during aging (Croll et al., 1998; Silhol et al., 2005). In summary, there is evidence that suggest that the BDNF-trkB system in the hippocampus is sensitive to aging.

BDNF AND ITS IMPACT UPON NEURONAL MORPHOLOGY

Transfection of granule cells from the DG with BDNF produces significant increases in axonal branch and basal dendrite numbers relative to empty vector controls. In addition, it has been shown by the same group that these structural changes could be prevented by the tyrosine kinase inhibitor K252a (Danzer et al., 2002). Thus, an increased expression of BDNF is sufficient to induce these morphological changes and it is likely that these morphological alterations are induced by an activation of trkB receptors. Results obtained by using mice that over-express BDNF confirmed these observations, since an increase in the dendrite complexity of DG cells could be observed in these mice (Tolwani et al., 2002).

BDNF, however, has not only an impact upon the branching pattern of hippocampal neurons. It has been demonstrated that BDNF is capable of increasing spine density in apical dendrites of CA1 neurons in slice cultures (Tyler and Pozzo-Miller, 2003; Alonso et al., 2004). Conditional trkB-deficient mice display a reduction in spine densities within the hippocampus (von Bohlen und Halbach et al., 2006a), indicating that BDNF-trkB signaling plays a critical role in the maintenance of dendritic spines within the hippocampus. In heterozygous trkB-deficient mice, a reduction in dendritic spines has also been noted (but to a lower extent) and – in addition – there is a further reduction in dendritic spine densities in aged heterozygous trkB mice (von Bohlen und Halbach et al., 2008). Therefore, BDNF via its action through trkB receptors has profound effects upon the morphology of hippocampal neurons.

DOES BDNF INFLUENCE TRANSMITTER-SYSTEMS PROJECTING TOWARDS THE HIPPOCAMPUS?

BDNF, acting through trkB receptors, is known to enhance growth and survival of serotonergic neurons (Galter and Unsicker, 2000; Mattson et al., 2004). In the adult rat brain, BDNF is able to promote regenerative sprouting of serotonergic fibers, but not the survival of injured serotonergic axons (Mamounas et al., 2000). In aged heterozygous BDNF^{+/−} mice the age-related loss of serotonin axons in the hippocampus was potentiated as compared to age-matched wild-type mice (Luellen et al., 2007), indicating that BDNF may play a role in the maintenance of the serotonergic system.

The noradrenergic system is also sensitive to aging. Exogenous BDNF infusion in rats caused a marked increase in the density of noradrenergic axons in the aged frontal cortex, whereas no trophic action of BDNF was observed in young and middle-aged brains (Matsunaga et al., 2004). Neutralization of endogenous BDNF with specific antibody to BDNF led to a reduction in noradrenergic axons in the frontal cortex of aged rats (Matsunaga et al., 2004). Furthermore, it has been shown that aged BDNF^{+/−} mice showed reduced numbers of cell bodies and fibers in the locus coeruleus compared with age-matched wild-type mice (Luellen et al., 2007).

These data, as well as others (Matsunaga et al., 2004, 2006; Traver et al., 2006) suggest that BDNF is necessary for the maintenance of noradrenergic innervations in the aged brain.

BDNF is also known as a neurotrophic factor for DAergic neurons of the substantia nigra (Hyman et al., 1991; Hagg, 1998; Dluzen et al., 1999). Inhibition of BDNF expression (Porritt et al., 2005) as well as a reduction of trkB expression (Zaman et al., 2004) can cause a loss of nigral DAergic neurons. The DAergic system is also sensitive to aging; thus, there is a reduction in the number of DAergic neurons during aging. This age-related cell loss is increased in aged heterozygous trkB mutant mice (von Bohlen und Halbach et al., 2005).

BDNF can promote the survival of developing cholinergic forebrain neurons and is able to attenuate the loss of neurons following excitotoxic lesions (Burke et al., 1994). Concerning the cholinergic innervation of the hippocampus, it has been shown that young BDNF^{−/−} mice have a reduced cholinergic innervation as compared to age-matched controls (Ward and Hagg, 2000) as well as reduced numbers of cholinergic cells in the medial septum that is accompanied by a decrease in the activity of choline acetyltransferase in the hippocampus (Grosse et al., 2005). Comparable to these results, it also has been shown that mice with reduced BDNF expression display decreased choline acetyltransferase activity (Chourbaji et al., 2004).

Thus, BDNF is capable of influencing the transmitter systems projecting towards the hippocampus.

BDNF IS INVOLVED IN HIPPOCAMPAL NEURONAL PLASTICITY

BDNF at low nanomolar range exited neurons in the cerebellum, cortex and hippocampus as rapidly as the neurotransmitter glutamate (Kafitz et al., 1999). Moreover, application of BDNF produces a sustained enhancement of synaptic strength at Schaffer collateral-CA1 synapses and this enhancement can be blocked by K252a (Kang and Schuman, 1995). The induction of LTP increases BDNF mRNA (Castren et al., 1993) as well as trkB mRNA (Dragunow et al., 1997) in the DG. In addition, it has been shown that hippocampal LTP and spatial learning are impaired in mice lacking BDNF (Korte et al., 1995; Linnarsson et al., 1997) as well as in mice lacking trkB (Minichiello et al., 1999).

Collectively, these data indicated that BDNF via trkB plays an essential role in neuronal plasticity within the hippocampus. Along this line it has been shown in 2008 that BDNF is necessary and sufficient to induce long-lasting structural changes at dendritic spines that are associated with synaptic plasticity (Tanaka et al., 2008). Thus, BDNF seems to play an important role in synaptic plasticity, probably through induction of morphological changes.

Based on the age-related decline in the expression of BDNF and trkB in the hippocampus, one would expect that BDNF-induced LTP may be weaker in aged than in adult animals. Concerning this, it has been shown that in aged rats, BDNF-LTP is significantly impaired within the hippocampus and that the activation of trkB is reduced in hippocampal tissue derived from aged rats (Gooney et al., 2004).

Given the importance of BDNF for spatial learning and synaptic plasticity, it is not surprisingly that adult heterozygous BDNF-deficient mice have problems in solving spatial tasks such as the Morris water maze (Linnarsson et al., 1997). Given the age-dependent

reduction in the BDNF-system, aged heterozygous BDNF-deficient mice should have great problems to solve spatial memory tasks. Indeed, by comparing adult and aged heterozygous BDNF knockout mice with age-matched BDNF$^{+/+}$ mice, Linnarsson et al. (1997) could show that aged wild-type mice performed significantly worse than young wild-type mice and the effect was even more pronounced in the aged BDNF mutant mice, which did not learn at all.

BDNF AND HIPPOCAMPAL VOLUME

The above-mentioned involvements of BDNF in structural changes and in neuronal plasticity in the hippocampus could indeed hint that BDNF via trkB has an impact upon hippocampal volume. Since BDNF seems also to be involved in several age-related alterations within the hippocampus, it is possible that age-related changes in hippocampal volume will be influenced by the action of this neurotrophin.

In humans, several polymorphisms of the BDNF gene have been discovered, as e.g. the functional Val66Met polymorphism in the coding region of the BDNF gene. Currently, there is a controversy whether the Val66Met polymorphism is associated with hippocampal volume change and depression or schizophrenia (Szeszko et al., 2005; Jessen et al., 2009; Koolschijn et al., 2009; Toro et al., 2009; Benjamin et al., 2010). However, there are reports indicating that the BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects (Bueller et al., 2006; Erickson et al., 2010). Thus, reduced levels or lack of functional BDNF may contribute to volume reductions in the hippocampus. Data obtained from heterozygous BDNF knockout mice indicate a hippocampal volume reduction (Lee et al., 2002; Magarinos et al., 2010), likewise heterozygous trkB mice also display a reduction in hippocampal volume (von Bohlen und Halbach et al., 2003). Based on these results it can be speculated that there is a link between hippocampal volume and BDNF, but is BDNF associated with age-related declines in hippocampal volume? This question is answered by a study from Erickson and coworkers. They found that increasing age was associated with smaller hippocampal volumes, reduced levels of serum BDNF, and poorer memory performance in humans. According to their results, reduction in hippocampal volume mediates the age-related decline in spatial memory and BDNF mediates the age-related decline in hippocampal volume (Erickson et al., 2010). Thus, there is evidence to suggest that BDNF is a critical player, involved in the maintenance of the hippocampal volume in the adult hippocampus. Such a role for BDNF may not only be postulated for hippocampal volume changes seen during aging, but may also be proposed for hippocampal volume changes that are associated with psychopathological conditions.

BDNF AND ALZHEIMER DISEASE

Alzheimer's disease and Parkinson's disease are the most common age-related degenerative disorders of the human brain. A hallmark of Alzheimer's disease is the progressive reduction of the hippocampal volume and stereological investigations have confirmed the substantial hippocampal cell loss seen in AD (West et al., 2000; Price et al., 2001).

Alzheimer's disease is further characterized by a strong reduction of the cholinergic innervation of the brain, including the hippocampus, and the occurrence of beta-amyloid plaques and Tau/neurofibrillary tangles. The plaques are mainly composed of amyloid beta-peptide (Aß), a 40–42 amino acid fragment of the beta-amyloid precursor (APP), whereas the tangles are mainly composed of helical filament of hyperphosphorylated tau.

Concerning a possible role of BDNF in Alzheimer's disease, there is a controversy, whether polymorphisms in the BDNF gene are associated with Alzheimer's disease. Thus, there are reports indicating that there exists an association between the BDNF gene polymorphisms and Alzheimer's disease (Kunugi et al., 2001; Ventriglia et al., 2002; Feher et al., 2009), whereas other groups did not find an association in various populations (Combarros et al., 2004; Nishimura et al., 2004; Li et al., 2005; He et al., 2007).

Concerning the hippocampus, it has been shown that BDNF mRNA expression (Phillips et al., 1991; Murray et al., 1994) as well as BDNF protein (Connor et al., 1997) are decreased in individuals that had suffered from Alzheimer's disease. Post-mortem brains from Alzheimer's disease patients display an absence of BDNF in reactive glia cells of microglia cells (Soontornniyomkij et al., 1999) and an absence of BDNF in neurons containing neurofibrillary tangles, whereas most neurons, intensely immunoreactive for BDNF, did not exhibit massive neurofibrillary degeneration (Murer et al., 1999). Thus, the age-related decline in BDNF could contribute to age-related changes seen in conditions of normal aging, whereas further disturbances in the BDNF-system may be related to pathological changes in the brain. Along this line, there is not only evidence to suggest that disturbances in the hippocampal BDNF-system contribute to neurodegenerative diseases, as e.g. Alzheimer's disease, but also to psychopathological conditions, as e.g. depression.

BDNF AND DEPRESSION

Depression is a disorder of the representation and regulation of mood and emotion. Depression has profound impact upon several brain structures, as e.g. the hippocampal formation (Campbell and Macqueen, 2004). Concerning the hippocampus, several groups have reported that the hippocampal volume is smaller in depressed patients as compared to controls (Mervaala et al., 2000; Frodl et al., 2002; Lange and Irle, 2004). An interesting aspect of antidepressant treatment is that it is capable of blocking or reversing hippocampal atrophy that is observed in patients with depression (Schmidt and Duman, 2007). The dendritic spines represent a possible anatomical substrate for the depression-induced changes in the hippocampus. A variety of studies indicate that depression is accompanied by reductions in dendritic arborization (Lucassen et al., 2006) and in the spine densities within the hippocampus and that treatment with antidepressants can ameliorate or reverse these reductions in spine densities (Norrholm and Ouimet, 2001; Pittenger and Duman, 2008; Hajszan et al., 2009). Moreover, in animal models of depression ("learned helplessness"), an exacerbated age-related loss of serotonergic fiber density in area CA1 has been observed (Aznar et al., 2010).

Antidepressant treatment increases hippocampal BDNF mRNA expression (Garza et al., 2004) as well as BDNF-immunoreactivity (Chen et al., 2001). In addition, BDNF produces antidepressant effects in behavioral models of depression (Shirayama et al., 2002). Moreover, activation of trkB receptors is induced by antidepressant drugs and this receptor activation is required for antidepressant-induced behavioral effects (Saarelainen et al., 2003). Since BDNF is capable of increasing dendritic spine densities, it is likely that BDNF has a beneficial effect upon the disturbed neuronal plasticity seen in

depression. Antidepressant treatments may, through enhanced BDNF signaling, improve the ability of critical brain circuits to respond optimally to environmental demands, a process that may be critical in the recovery from depression (Castren and Rantamaki, 2008) and drugs that selectively stimulate the production of neurotrophins could represent a new generation of antidepressants (Altar, 1999).

SUMMARY

BDNF is required in the postnatal brain, playing an important role in the maintenance of the brain architecture. Reductions in BDNF, seen either during normal aging, or in pathological conditions, are related to declines in neuronal plasticity and changes in the morphology of hippocampal neurons. These alterations could result in hippocampal dysfunctions and could contribute to hippocampal atrophy, seen during normal aging or in Alzheimer's disease. Concerning depression, a variety of studies suggests a critical role of neurotrophins, such as BDNF, in regulating neuronal morphology and neuronal plasticity. Alterations in neuronal plasticity accompanied by changes in the architecture of the hippocampus are also observed during normal aging (**Table 1**). Since there is an age-related decline in the expression of BDNF and since alterations in BDNF levels have effects upon the morphology of hippocampal neurons as well as on hippocampal neuronal plasticity, BDNF may represent a candidate that plays a critical role in age-related changes, at least in the hippocampus.

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Table 1 | Changes in the hippocampus or in hippocampus-dependent functions.

	Aging	Alzheimer disease	Depression	trkB- or BDNF-deficient mice
Hippocampal volume	Reduced	Reduced	Reduced	Reduced
Loss of hippocampal neurons	No	Yes	No	Minor
Hippocampal spine densities	Reduced		Reduced	Reduced
Neurogenesis	Reduced	Increased [1]	Reduced	Reduced [2]
LTP	Reduced	Reduced [3]	Reduced [4]	Reduced
Spatial learning	Reduced	Reduced [5]	Reduced [6]	Reduced

Several of these alterations are also seen in trkB- or BDNF-deficient mouse models.
[1]*Jin et al. (2004).*
[2]*As determined by a trkB-deficient mouse line (Li et al., 2008).*
[3]*Data from mouse models of AD (Nalbantoglu et al., 1997; Smith et al., 2009; Auffret et al., 2010; Gengler et al., 2010).*
[4]*Data from "learned helplessness," an animal model of depression (Ryan et al., 2009).*
[5]*Data from mouse models of AD (Moran et al., 1995; Nalbantoglu et al., 1997; Gordon et al., 2001).*
[6]*Data from "learned helplessness" (Song et al., 2006).*

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